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EXAMINER	
LIU, SAMUEL W	

ART UNIT	PAPER NUMBER
1656	

NOTIFICATION DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

usptomailnyc@kslaw.com

Office Action Summary	Application No.	Applicant(s)	
	10/591,485	WAUGH ET AL.	
	Examiner	Art Unit	
	SAMUEL LIU	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 October 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *78-80,84,85,88 and 90-97* is/are pending in the application.

4a) Of the above claim(s) *95* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *78-80,84,85,88,90-94,96 and 97* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 September 2006* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :1/24/08, 3/24/08, 10/7/08, 7/6/09, 7/22/09 & 10/5/10.

DETAILED ACTION

Status of claims

Claims 78-80, 84, 85, 88, and 90-97 are pending.

The preliminary amendment filed 11/7/07, which cancels claims 1-77, 81-83, 86, 87, 89, and 98-240, amends claims 78-80, 84, 85, 88 and 90-97 has been entered.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119 (a)-(d) based on an application 10793138 filed in United States of America on 4/15/08.

IDS

The references cited in the information disclosure statements (IDSs) filed 1/24/08, 3/24/08, 10/7/08, 7/6/09, 7/22/09, and 10/5/10 have been considered by Examiner.

Election/restriction

Applicants' election (filed 10/5/10) of Group I (claims 91-94, 96 and 97) with traversal is acknowledged. Group 1 is drawn to a method of providing an aesthetic effect to a subject in need thereof comprising administering to the subject in need thereof a botulinum toxin, and additional election of Botulinum toxin type A The traverse is on the ground that Rothbard does not destroy the unity of applicants' claims because Rothbard does not teach/suggest a positively charged backbone having attached positively charged branching group. This is found unpersuasive because, as discussed in the restriction requirement mailed 4/5/10, Rothbard et al. (WO0162297) teach a method of transdermally (patent claims 1, 21 and 25) delivering to a subject a composition comprising a biological compound, e.g., antibacterials, antivirals and/or hormone (patent claim 20) with positively charged arginine (patent claims 1, 7 and 10) as delivery-enhancing transportor, wherein the transportor is a branched configuration using, for example, a lysine residue to form a branch in a peptide configuration (p.11, lines last 3 lines), and wherein α-amino group (positively charged) is a part of the arginine backbone thereby the backbone is positively charged while guanidinium group (positively charged) is considered to be the positively-charged branching group branched from the backbone. Therefore, the claimed

method (at least claim 78, a *linking* claim) does not constitute a special technical feature as defined by PCT Rule 13.2 and 37 CFR 1.475(a), as a single contribution over the art, and a holding of lack of unity is therefore proper. Therefore, the requirement is still deemed proper and is therefore made FINAL.

Group II, claims 91-94, 96 and 97 drawn to a method providing an cosmetic effect to a subject is under consideration and examined together with Group I, claims 91-94, 96 and 97 drawn to a method providing an aesthetic effect to a subject. The restriction between Groups I and II is withdrawn. Group III, claim 95 (Group 3) is withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Because applicants elected "Botulinum Toxin type A" (claim 91 for examination, the botulinum toxin serotypes B, C, D, E, F and G other than serotype A set forth in claim 91 are withdrawn from further consideration. Therefore, claims 91-94, 96 and 97 and elected "Botulinum Toxin type A" are under examination.

Objection to specification

The disclosure is objected to because of the following informalities:

(1) At page 15, [0038], the brief description of Figures 3 and 4 should indicate the meanings of the terms: "AL1", AK1", and "AM1" becasue these terms have been depicted in Figures 3 and 4without clear definition/description. Similarly, see also, "AL" and "ALK" in Figure 5; "AS, "AT" and "AU" in Figure 6; and "EB-btox" and "Nl" in Figure 7.

(2) At page 15, [0043], line 1, "Figure 9" should be changed to "Figure 9A to 9-D".

Objection to the drawings

The drawing filed 9/1/06 is objected to under 37 CFR 1.83(a) because of the following:

It appears that drawing at page "8/12" (per the drawing set) lacks label as "Figure 8".

Corrected drawing sheets in compliance with 37 CFR 1.121(d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if

only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as "amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 79, 80, 84, 85, 88 and 90- 97 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 79, the recitation "wherein the composition" lacks antecedent basis in claim 78 from which claim 79 depends. Claims 80, 84, 85, 88 and 90- 97 which depend from claim 79 are also rejected.

Also, in claim 90, the recitation "the therapeutic protein" lacks antecedent basis in claims 80, 79 and 78 from which claim 90 depends.

Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

[1] Claims 78-80, 84, 88, 90, 93, 94, 96 and 97 are rejected under 35 U.S.C. 102(b) as being anticipated by Waugh et al. (WO0207773 A3, from IDS).

Waugh et al. discloses delivery (administering) the therapeutic agent (see abstract, and p.4, lines 6-8) wherein the agent form a non-covalent association complex with a positively-charged backbone compound (p.3, lines 17-18 and 30-34), wherein the positively-charged backbone compound is a polypeptide such as polylysine (p.8, lines 1-2 and 6-9), and has covalently attached efficiency group (equivalent to instant "*positively charged carrier*") (p.4, lines 2-3, and Fig. 1) which is positively charged moiety such as $(Gly)_{n1}$-$(Arg)_{n2}$ (n1 and n2 is from 3-5, and 7-17, respectively (see p.5, lines 25-30, and p.9, lines 17-28). Said therapeutic agent is a cell receptor ligand for a cell surface receptor (see p.12, lines 22-24), and more particularly, the preferred therapeutic agent is botulinum toxin (BOTOX) (see p.16, lines 1 and 14, and p.17, lines 7-8). Topical administration to skin and/or mucous membrane (equivalent to instant epithelium) is used (p.18, line 33-34, and p.19, line 4),

The composition comprises the therapeutic agent and the complex of positive charge (p.18, lines 24-27) is suitable for transdermal administration (p.18, line 33 to p.19, line 1, and Figures 3-10).

Because structural feature is inherent property of a biomolecule, said composition must have greater transdermal delivery ability as compared to the agent in the absence of the attached

efficiency group, i.e., "*positively charged carrier*" (claim 79). It is of note that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

The above Waugh et al. teachings anticipate claims 78, 79, 80, 84, 90 and 96.

The composition is administered via a sustained-release (see p.20, lines 21-26) route to skin which is considered to be equivalent to instant the face/surface of a subject administered (claim 96) or to mucous membrane i.e., inside mouth which is considered to be equivalent to instant to the subject other than the face /surface (claim 97) (see p.19, line 4). Thus, claims 88, 96 and 97 are rejected.

Claim 93 is included in the rejection, because without setting forth specific structural limitation to the botulinum toxin polypeptide, the recombinant botulinum toxin is considered to have identical structure to native toxin thereof.

Waugh et al. teach that the botulinum toxin is a cosmeceutic agent as well, which anticipates claim 94.

[2] Claims 78-80, 84 and 88 are rejected under 35 U.S.C. 102(b) as being anticipated by Rothbard et al. (WO0162297 A1, from IDS).

CLAIM INTERPRETATION: claim 78 as written is broadly drawn to a method of administering a bioactive protein non-covalently associated with a positively charged carrier which constitute two parts: a positively charged backbone (peptide backbone without side chain reads on this) and a positively charged branching group conjugated to said backbone.

Rothbard et al. teach a method of topically delivering by a transdermal patch (patent claims 1, 24 and 25) to a subject a composition comprising a therapeutic agent (patent claims 26) such a peptide hormone vasopressin (patent claim 31) and a delivery-enhancing transportor which contains positively charged moieties such as guanidine or amidino groups (patent claims 1 and 6). Interaction between the agent and the transportor is non-covalent (p.23, lines 5-8). Said transportor is a branched configuration using, for example, a lysine residue to form a branch in a peptide configuration (p.11, lines last 3 lines), and wherein α-amino group (positively charged) is a part of the arginine backbone thereby the backbone is positively charged while guanidinium group (positively charged) is considered to be the positively-charged branching group branched from the backbone. These teach instant claim 78.

Because structural feature is inherent property of a biomolecule, said composition must have greater transdermal delivery ability as compared to the agent in the absence of the attached efficiency group, i.e., "*positively charged carrier*" (claim 79). It is of note that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

Thus, the above Rothbard et al. teachings anticipate instant claims 78, 79, 80 and 84.

Sustained-release formulation is used (p.27, 3rd paragraph, line 4), which anticipates claim 88.

Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

[1] Claim 85 is rejected under 35 U.S.C. 103(a) as being unpatentable over Waugh et al. (WO0207773 A3) in view of Crowley et al. (US 20030109448).

Because claim 85 depends from claims 78, 79 and 80, these claims are included in the rejection herein.

Waugh et al. discloses delivery (administering) the therapeutic agent (see abstract, and p.4, lines 6-8) wherein the agent form a non-covalent association complex with a positively-charged backbone compound (p.3, lines 17-18 and 30-34), wherein the positively-charged backbone compound is a polypeptide such as polylysine (p.8, lines 1-2 and 6-9) or polymer such as poly(propylene amine) (see p.7, lines 19-21), and has covalently attached efficiency group (equivalent to instant "*positively charged carrier*") (p.4, lines 2-3, and Fig. 1) which is positively charged moiety such as $(Gly)_{n1}$-$(Arg)_{n2}$ (n1 and n2 is from 3-5, and 7-17, respectively (see p.5, lines 25-30, and p.9, lines 17-28). Said therapeutic agent is a cell receptor ligand for a cell surface receptor (see p.12, lines 22-24), and more particularly, the preferred therapeutic agent is

botulinum toxin (BOTOX) (see p.16, lines 1 and 14, and p.17, lines 7-8). These are applied to claims 78 and 80.

The composition comprises the therapeutic agent and the complex of positive charge is suitable for transdermal administration (p.18, line 33 to p.19, line 1). Because structural feature is inherent property of a biomolecule, said composition must have greater transdermal delivery ability as compared to the agent in the absence of the attached efficiency group, i.e., "*positively charged carrier*" (claim 79). It is of note that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. Therefore, claim 79 is anticipated.

Provided that Waugh et al. do not expressly teach separate adminstyeration of the therapeutic protein and the positively-charged compound (carrier).

Waugh et al. teach that suitable methods of administering the therapeutic composition/compound are well known to those of skill in the art, and, that a variety of administration methods can be used for delivering the composition of interest to a subject (see p.19, lines 21-29) wherein said "a variety of administration" encompasses the "separate administration. Moreover, the separate administration for the pharmaceutical composition is known in the art (see [0057], US 20030109448) at the time instant application was filed. Theses are applied to claim 85.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the administration route because the separate administration of the

pharmaceutical composition has been well known in the art (see above), and because Waugh et al. have taught that there are a variety of administration methods for delivering the disclosed composition comprising therapeutic protein/agent and the positively-charge carrier. Said determination thus would have been well within the purview of one or ordinary skill in the art (pharmacology), and therefore, said separate administration are considered to be *prima facie* obvious in the absence of any unexpected result.

[2] Claims 91 and 92 are rejected under 35 U.S.C. 103(a) as being unpatentable over Waugh et al. (WO0207773 A3) in view of Aoki et al. (EP 1421948, from IDS).

Since claim 85 depends from claims 78, 79, 80 and 90, these claims are included in the rejection herein. The rejection of claims 78, 79 and 80 by Waugh et al. has been set forth above wherein said rejection is also applicable to claim 90 since Waugh et al. have taught that the therapeutic protein is the botulinum toxin (claim 90).

Provided that Waugh et al. do not expressly teach the serotype or form of the botulinum toxin.

Aoki et al. teach different serotypes of the botulinum toxin (BT), e.g., serotype A (see abstract and Table 1) useful for relieve pain in a patient or treating a smooth muscle disorder by administering to said patient the BT polypeptide (see [0014]), and teach use BT derivative "BOTOX®" (see [0027], line 3), as applied to claims 91 and 92.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to choose suitable serotype of BT for certain therapeutic use. This is becasue the structure and usefulness of said BT polypeptide including the BT derivative has been known in

the art (see above) at the time instant application was filed, and because one of ordinary skill in the art, e.g., physician would have become more familiar with the use of the BT product disclosed by Aoki et al. and would have chosen appropriate BT molecule (see [0027]). Further, in view of feasible treatment of various disorders as set forth in Examples 1-11 by BT or by the BT derivative, one of ordinary skill in the art would have appropriately used certain BT serotype with reasonable expectation of success. Thus, the combination of the references' teachings renders the claims *prima facie* obvious in the absence of any unexpected results.

[3] Claim 85 is rejected under 35 U.S.C. 103(a) as being unpatentable Rothbard et al. (WO0162297 A1) in view of Crowley et al. (US 20030109448) and Waugh et al. (WO0207773 A3).

Because claim 85 depends from claims 78, 79 and 80, these claims are included in the rejection herein.

Rothbard et al. teach a method of topically delivering by a transdermal patch (patent claims 1, 24 and 25) to a subject a composition comprising a therapeutic agent (patent claims 26) such a peptide hormone vasopressin (patent claim 31) and a delivery-enhancing transportor which contains positively charged moieties such as guanidine or amidino groups (patent claims 1 and 6). Interaction between the agent and the transportor is non-covalent (p.23, lines 5-8). Said transportor is a branched configuration using, for example, a lysine residue to form a branch in a peptide configuration (p.11, lines last 3 lines), and wherein α-amino group (positively charged) is a part of the arginine backbone thereby the backbone is positively charged while guanidinium

group (positively charged) is considered to be the positively-charged branching group branched from the backbone. These are applied to instant claim 78.

Because structural feature is inherent property of a biomolecule, said composition must have greater transdermal delivery ability as compared to the agent in the absence of the attached efficiency group, i.e., "*positively charged carrier*" (claim 79). It is of note that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01. This is applied to instant claims 78 and 79.

Provided that Waugh et al. do not expressly teach separate adminstyeration of the therapeutic protein and the positively-charged compound (carrier).

Crowley et al. teach separate administration for the pharmaceutical composition is well known in the art (see [0057], US 20030109448). Waugh et al. teach that suitable methods of administering the therapeutic composition/compound are well known to those of skill in the art, and, that a variety of administration methods can be used for delivering the composition of interest to a subject (see p.19, lines 21-29) wherein said "a variety of administration" encompasses the "separate administration, as applied to instant claim 85.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to determine the administration route because the separate administration of the pharmaceutical composition has been known in the art as taught by Crowley et al. (see above), and because Waugh et al. have taught that there are a variety of administration methods for

delivering the disclosed composition comprising therapeutic protein/agent and the positively-charge carrier. Said determination thus would have been well within the purview of one or ordinary skill in the art (pharmacology), and therefore, said separate administration are considered to be *prima facie* obvious in the absence of any unexpected result.

Provisional Rejection -Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

[1] Claims 78-80, 84, 85, 90-94, 96 and 97 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 67-70 and 72 of Application No. 10591486 ('**486**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 67-70 and 72 of '486 disclose topically administering via transdermal route to a subject skin a bioactive protein which has therapeutic activity (e.g., botulinum toxins, claim 70

of '486) and is associated with a carrier that comprises a positively charged polypeptide containing the positively charged branching groups wherein said association between the protein and the carrier is non-covalent. This is the common subject matter of instant claims 78-80, 84, 85, 90-93, 96 and 97.

Since "provide a cosmetic benefit to the subject" (instant claim 94) is considered to be inherent property of the biological agent such as botulinum toxin, claim 94 is included in the rejection.

[2] Claims 78-80, 84, 85 and 90-94 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-30 and 33 of Application No. 12897188 ('**188**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 28-30 and 33 of '188 disclose a method for transdermally delivering a biological agent to a cell in a subject comprising administering to said subject a composition comprising (a) a positively charged backbone containing groups carrying a positive charge extending from the backbone (page 7, lines 14-16, the specification of '188), and (b) a biological agent having negatively charge, i.e., non-covalent interaction between (a) and (b); wherein the biological agent includes polypeptide such as growth hormone and botulinum toxin (BOTOX) (see page 15, lines 21-22 and 34-35, and page 16,line 14, the specification of '188); which is an obvious variation of instant claims 78-80, 84, 85, and 90-93.

Since "provide a cosmetic benefit to the subject" (instant claim 94) is considered to be inherent property of the biological agent such as botulinum toxin, claim 94 is included in the rejection.

[3] Claims 78-80, 84, 85, 88, 90-94, 96 and 97 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 51-54, 64, 77, 78, 80 and 110 of Application No. 10591732 ('**732**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 51-53 of '732 disclose topically administering to skin or epithelium or face (claim 64 of '732) of a subject the botulinum toxin (BT) (e.g., serotype A, claim 80 of '732) or BT derivative or recombinant BT (claims 77 and 78 of '732) in conjunction with a positively charged carrier that comprises a positively charged backbone and branching groups, wherein the association between the carrier and the BT is non-covalent, which is the common subject matter of instant claims 78-80, 84, 90-93, 96 and 97.

Claims 54 and 55 of '732 disclose the same subject mater as instant claim 94.

Claim 110 of '732 discloses a controlled release for the administration, which is the common subject matter of instant claim 88.

[4] Claims 78-80, 84, 85, 90-94, 96 and 97 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9, 13-16 and 21-24 of Application No. 11816602 ('**602**). This is a provisional double patenting rejection because the

conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 9, 13-16 and 21-24 of '602 disclose treating wrinkles comprising administering to skin of a patient a formulation that comprises a botulinum toxin (BT), e.g., serotype A, or BT derivative "BOTOX®" see [0055] of '602), wherein the BT or BT derivative is non-covalently complexed with the positively charged backbone wherein said backbone further comprises positively charged efficiency groups (claims 13 and 21-24 of '602) equivalent to instant branching groups. This discloses the common subject matter of instant claims 78-80, 84, 85, 90-93, 96 and 97.

Since "provide a cosmetic benefit to the subject" (instant claim 94) is considered to be inherent property of the BT ([0022], lines 11-13, '602), claim 94 is included in the rejection.

[5] Claims 78-80, 84, 85, 90-94, 96 and 97 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15 of Application No. 11954885 ('**885**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claim 15 of '885 discloses treating a disease by transdermally administering a conjugate to a target cell (i.e., a subject), wherein the conjugate comprises (i) a cargo molecule and (ii) a transport molecule wherein interaction between (i) and (ii) is non-covalent, wherein the transport molecule contains a positively charged polypeptide covalently attached to a positively charged backbone that is non-covalently bound to the cargo molecule (claims 1, 3 and 4 of '885); and

wherein the cargo molecule is a therapeutic polypeptide such as a serotype of botulinum toxin (claims 11-13, of '885). The transport molecule has ability of increasing the penetration of the cargo molecule through a biological membrane in the skin (claims 5 and 6 of '885) which is equivalent to effect of instant topical administration to the face or to a site other than the face of the subject as set forth in instant claims 96 and 97. These disclose the common subject matter of instant claims 78-80, 84, 85, 90-93, 96 and 97.

Since "provide a cosmetic benefit to the subject" (instant claim 94) is considered to be inherent property of the BT, claim 94 is included in the rejection.

[6] Claims 78-80, 84, 85, 90-94, 96 and 97 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15 of Application No. 12520964 ('**964**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claim 15 of '964 discloses treating a disease by transdermally administering a conjugate to a target cell (i.e., a subject), wherein the conjugate comprises (i) a cargo molecule and (ii) a transport molecule wherein interaction between (i) and (ii) is non-covalent, wherein the transport molecule contains a positively charged polypeptide covalently attached to a positively charged backbone that is non-covalently bound to the cargo molecule (claims 1, 3 and 4 of '885); and wherein the cargo molecule is a therapeutic polypeptide such as a serotype of botulinum toxin (claims 11-13, of '885). The transport molecule has ability of increasing the penetration of the cargo molecule through a biological membrane in the skin (claims 5 and 6 of '885) which is

equivalent to effect of instant topical administration to the face or to a site other than the face of the subject as set forth in instant claims 96 and 97. These disclose the common subject matter of instant claims 78-80, 84, 85, 90-93, 96 and 97.

Since "provide a cosmetic benefit to the subject" (instant claim 94) is considered to be inherent property of the BT, claim 94 is included in the rejection.

[7] Claims 78-80, 84, 85, 90-94, 96 and 97 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 and 9 of Application No. 12647677 ('**677**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 1-5 of '677 disclose administering botulinum toxin (BT), e.g., serotypes A, in order to achieve a therapeutic or cosmetic effect to an individual in need thereof comprising injection) (a topical route) of a composition which comprises a positively charged carrier that contains a positively charged backbone with plurality of efficiency groups attached thereto, wherein said backbone is polyamino acid such as polylysine and wherein the efficiency groups are positively charged molecule such as $(gly)_{n1}$-$(arg)_{n2}$. BT can be derivative thereof such as "BOTOX®" (claim 9, of '677). These disclose the common subject matter of instant claims 78-80, 84, 85, 90-94, 96 and 97.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Liu whose telephone number is (571)272-0949. The examiner can normally be reached on Monday-Friday, 9 am to 5:30 pro. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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/Samuel W. Liu/
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